

Please amend the subject application as follows:

AMENDMENTS TO THE SPECIFICATION

Please replace the subtitle on page 6, line 1 with the following amended subtitle:

4. FIGURES BRIEF DESCRIPTION OF THE DRAWINGS

Please replace the paragraph beginning at page 6, line 2 with the following amended paragraph:

~~Figure Fig.~~ Fig. 1 shows a representative estimation of arsenic level versus time curve (AUC) attributed to intravenous and oral dosing with arsenic trioxide in a single patient. All AUCs were computed using the trapezoid rule. The net 24 h AUC attributable to oral dosing was calculated as the difference between the gross 24-48 h AUC on day 2 and the corresponding AUC attributable to intravenous dosing. The latter AUC was calculated using the extrapolated arsenic level derived from estimates of that patient's elimination pharmacokinetics on day 1 (see Table IV). ~~Figure Fig.~~ Fig. 1 is adopted from Kumana *et al.*, *Eur J Clin Pharmacol.* ~~2002;58:521-6~~ (2002) 58:521-6, which is incorporated herein by reference in its entirety.

Please replace the paragraph beginning at page 6, line 10 with the following amended paragraph:

~~FIG. 2 shows~~ Figs. 2a-2i show the arsenic concentrations of all nine (9) patients in plasma and whole blood arsenic concentrations on day 1 and day 2. ~~FIG. 2 is~~ Figs 2a-2i are also adopted from Kumana *et al.*, *supra.*, which is incorporated herein by reference in its entirety.

Please replace the paragraph beginning at page 6, line 13 with the following amended paragraph:

~~Figure~~ Fig. 3 shows the clinicopathologic features and outcome of 12 consecutive patients with relapsed acute promyelocytic leukemia (APL) treated with oral As₂O₃. ~~Figure Fig. 3~~ is adopted from Au *et al.*, *Blood* ~~2003;102:407-8~~ (2003) 102:407-8, which is incorporated herein by reference.

Please replace the paragraph beginning at page 18, line 30 with the following amended paragraph:

To derive the 24 – 48 hour arsenic level versus time curve (AUC) attributable to the intravenous infusion, it was assumed that the elimination of arsenic eventually approximates to mono-exponential decay. On that basis, log arsenic concentration versus time plots of individual patients (covering periods up to 24 hours post intravenous dosing) were submitted to regression analysis, using customized computer software developed by The University of Hong Kong Computer Centre. The highest ensuing regression value (r^2) associated with a negative slope (indicating decaying concentration) was selected for subsequent calculations; all such computations being based on a minimum of 3 points. For example, if after intravenous dosing r^2 values for data sets from 1 – 24, 2 – 24, 3 – 24, 4 – 24 and 6 – 24 hours were 0.53, 0.62, 0.80, 0.95, and 0.94, respectively, then the data set from 4 – 24 hours would be used for the calculation, provided its slope was negative. From the selected data set, the following parameters were then generated: β -elimination phase first order elimination rate constant (K_e), elimination half-life ($T_{1/2}$), and extrapolated zero time concentration (C_0). For each patient, these parameters were used to estimate an extrapolated 24 – 48

hour AUC attributed to intravenous dosing. The difference between the latter AUC and the actual (or gross) 24 to 48 hour AUC (~~see Fig.~~ Figure 1) was regarded as the net 0 to 24 hour AUC attributable to oral dosing.

Please replace the paragraph beginning at page 21, line 5 with the following amended paragraph:

Four (4) patients had relapsed/refractory acute myeloid leukemia (AML), and five (5) had relapsed and acute promyelocytic leukemia (APL). None with refractory AML responded hematologically and all died subsequently from leukemia. All five (5) with relapsed APL achieved a complete hematological remission and were alive as of April, 2002; the median duration of survival since starting arsenic therapy being 11 months and since diagnosis 36 months (ranging 20 – 56 months). For three (3) patients (7, 8 and 9) with relapsed APL, rapid progression of their leukemia necessitated treatment before they refraining from seafood for an entire week. Figs 2a-2i illustrate ~~Figure 2 illustrates~~ the plasma and blood arsenic concentration versus time plots of the nine (9) patients studied. Concerning systemic bioavailability of our oral formulation of As_2O_3 , Table 3 summarizes the AUC findings with respect to IV and oral dosing. Table 4 lists the prevailing hemoglobin and hematocrit values of these patients at the time they were studied and the plasma and estimated cellular arsenic concentrations at 48-hours. On average, cellular As concentrations exceeded plasma concentration by 270 %.